

## A. Specific Aims

The goal of our research is to speed the translation of new cancer therapies to patients through the use of imaging biomarkers. Our basic hypothesis is that tools that allow non-invasive monitoring can facilitate mechanistic oncology studies in humans. Most therapy trials are not mechanistic: there is typically no clear understanding of why a given patient does or does not respond to a new (or old) treatment. Making the human the experimental organism should make the development of new therapies more efficient through earlier and more complete feedback; non-invasive imaging is a key methodology for such early feedback.

Imaging tools such as MRI, CT, and PET are already an essential part of routine cancer care but their role in the evaluation of therapeutic efficacy is evolving due to rapid changes in imaging technology and the relatively limited attention given to validation of imaging endpoints. Many groups, from NIH consensus conferences to the FDA in its Critical Path Initiative, have explicitly identified the promise of imaging innovations to speed drug development but also noted the complexity of these tools, and called for additional development and validation. To meet this need we propose our first specific aim: forming a partnership focusing on developing and qualifying cancer imaging biomarkers, with founding members including Massachusetts General Hospital, the Dana-Farber Cancer Center, Novartis, Siemens Medical Solutions, the US Food and Drug Administration, and two patient advocacy groups. This new partnership will facilitate a new level of interaction between the technical, medical, and drug development communities.

Imaging biomarkers are used to provide at least three types of information: (i) localized pharmacokinetic / pharmacodynamic (PK/PD) data, (ii) patient selection, and (iii) surrogate endpoints for either go/no-go decision-making or even for regulatory approval, though enthusiasm is tempered by some failures of imaging biomarkers. Because of the range of potential uses, each with varying risks, the scientific focus of our partnership will be to “qualify” (rather than “validate”) existing and novel imaging biomarkers. The term “qualify” reflects our view that the utility of a given biomarker is fully dependent on its intended use, and that a rigorous scientific approach is needed when evaluating and using biomarkers. We also see biomarkers for drug development having their own “pipeline” of development, ranging from an initial concept phase, when a biomarker might have only limited utility and large error bars, to a later phase when the strengths and weaknesses of an imaging biomarker are well-quantified. A goal of our partnership will be to identify these error bars for each biomarker as it moves through different stages of the biomarker pipeline.

To best speed cancer drug development, we will choose imaging biomarkers for testing that provide insight into mechanisms of cancer therapy that appear to be most promising. We seek to place this development and qualification process deep in an environment of oncology clinical research and care so as to ensure the relevance and timeliness of the tools. Our partnership’s steering committee has agreed therefore that our second specific aim is to select and execute compelling projects, which we will do on a “Project” (~\$150K/yr) and “Pilot Project” (~\$40K/yr) basis. Flexibility to new drugs and rapid evaluation of projects with a milestone-driven approach to funding will be a key feature of our AP4, and therefore predicting today how the first five years’ work will proceed is difficult. Nevertheless, we outline below three main projects and four pilot projects that appear to be the most promising at this point in time. These projects are:

**Project 1:** Mechanistic studies of bevacizumab (anti-VEGF antibody) combination therapy in rectal cancer using CT perfusion, <sup>18</sup>FDG-PET, tumor interstitial fluid pressure, and other correlates of anti-angiogenesis.

**Project 2:** Sorafenib (anti-RAF kinase, anti-VEGF small molecule) in soft-tissue sarcomas monitored with DCE-MRI, diffusion MRI, and <sup>19</sup>F-MR spectroscopy to determine early drug PK/PD and drug effect.

**Project 3:** Recurrent glioma treated with AZD2171 (anti-VEGF, c-kit small molecule) monitored with advanced MRI techniques (DCE, PWI, DTI) plus tissue and molecular correlation.

**Pilot Project 1:** Review of imaging biomarkers used by FDA in approving cancer biologics. Understanding what FDA has accepted in the past can help guide future selection and qualification of imaging biomarkers.

**Pilot Project 2:** Development of radiolabeled gemcitabine for human use. Tumor-specific PK/PD information could shed light on mechanisms of efficacy and resistance to gemcitabine.

**Pilot Project 3:** Labeling of T cells with a clinically used iron particle for MRI-based cell tracking. T cells are involved in many cancers and a high-resolution technique to track such cells would be a powerful tool.

**Pilot Project 4:** Correlation of tissue blood volume in renal cell cancer as measured with ferumoxtran-10 with histopathologic grade. Blood volume is a promising biomarker but direct correlation with grade is needed. Biomarkers qualified through this AP4 will speed not only the specific drugs investigated here but will be shared with the broader oncology community to accelerate therapy development as widely as possible.